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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/740,653	Applicant(s) METCALF ET AL.
	Examiner Mark L. Berch	Art Unit 1624

-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,13-28,30-62,64-98,100-116 and 118-259* is/are pending in the application.

4a) Of the above claim(s) *30,31 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,13-28,32-35,40-62,64-98,100-116 and 118-259* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Objections

Claims 30-31, and 36-39 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. Thus, all multiply dependent claims which depend on e.g. claim 19 are improperly multiply dependent. See MPEP § 608.01(n) ("a multiple dependent claim may not serve as a basis for any other multiple dependent claim, either directly or indirectly."). Thus for example, claim 30 is multiply dependent on both 20 and 25, and claim 20 is dependent on claim 19, which is itself multiply dependent. Accordingly, claims 30-31, and 36-39 have not been further treated on the merits.

Applicants submitted a set of references with no IDS. Some of them are cited on the 892. The other have insufficient information to properly cite. If applicants wish these made of record, they must provide a proper 1449.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 9, 14, 16, 18, 54, 112, 114, 122-123, and 175 are rejected under 35 U.S.C. 102(b) as being anticipated by Brush.

The reasons were given previously; the traverse is unpersuasive. The proviso excludes one or two P moieties, but this has three, and hence is not excluded.

Claims 1-5, 7, 9, 14, 17-18, 54, 112, 114, 116, 122-123, 175 are rejected under 35 U.S.C. 102(b) as being anticipated by Suhadolnik.

The reasons were given previously; the traverse is unpersuasive. Example 8 as noted has the derivatives with three P moieties.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 13-28, 32-35, 40-62, 64-98, 100-116, 118-259 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "aliphatic" has been rendered indefinite by the specification. Aliphatic means groups lacking in rings. See on this exact point *Ex Parte Clifford*, 63 USPQ 19. But page 11, line 6 says that aliphatic includes things with cycles, and cycloalkyl is listed; others appear at page 22, lines 18-20 etc. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Since applicants have obliterated the essential requirement for aliphatic, there is no way of knowing what the term means to exclude, since it appears to cover everything. Thus, e.g. claim 54's or claim 108's "cyclic ... aliphatic" is self-

contradictory and meaningless. For purposes of interpreting the proviso in claim 1, the term is understood in its full breadth as given in the specification. The traverse is unpersuasive. Applicants assert that the term does include rings, but that it contains only C and H. Applicants are incorrect in both regards. Groups which have only C and H are called hydrocarbons. Applicants have misunderstood the Nostrand's reference. Methane has no ring; derivatives of methane have no ring, but these could certainly have heteroatoms. Methyl chloride has a heteroatom and is absolutely a derivative of methane. The Nostrand's reference says nothing about being a hydrocarbon. There is cited the Hampel reference, which states clearly that these are compounds "whose carbon atoms are arranged in straight or branched chains" i.e. not rings. It gives as examples "aldehydes, ketones, alcohols", etc "which have no ring structure". Note that these have oxygen present, again disputing the notion that the term denotes hydrocarbon. There is also cited the Hackh's Chemical Dictionary, which says "Acyclic". It too gives as examples non-hydrocarbons, e.g. aliphatic acids. The reference The American Heritage® Dictionary of the English Language: Fourth Edition. 2000, entry for aliphatic says, "organic chemical compounds in which the carbon atoms are linked in open chains." As a result, the term "non-aromatic aliphatic" is also indefinite, as aliphatic cannot be aromatic in the first place; likewise "cyclic aliphatic" (e.g. claim 123, 199, etc.).

2. Likewise, the term "substituted or unsubstituted ... aliphatic" (e.g. in claim 3) makes no sense, as aliphatic already permits substituents.

3. The claim 1 provision for the P-moiety being a substituent on RD is no longer possible. RD is now only H, and H cannot have a substituent.

4. Similarly, it is unclear what "heteroaliphatic" means either. It appears to be any moiety which has an atom other than C and H. Is that what is intended? Given that applicants state that the sole requirement of aliphatic is that it have only C and H, the "hetero" then abolishes that sole requirement, so that it is left with no meaning at all. In this regard, Applicants state that the specification "limits the substitution to an oxygen, S, N, P or Silicon atoms." It most certainly does not. It says that these choices are "e.g.". Those are just examples of what the heteroatoms are, not the only choices.
5. The page 12 text of "wherein ... unsubstituted" is of unclear purpose. This appears to repeat what the specification already says, and hence, if it were to be removed, the scope of the claim would be the same. Hence, its function is unknown. The traverse is unpersuasive. This is not a matter of simple double inclusion. It might also be attempting to say that the substituents themselves can be substituted.
6. In next to last line of claim 202, that should be "an aryl".
7. The last line of claim 122 is of unknown purpose. OH is already a permitted substituent, so that if those "optionally substituted" claim language were removed, the scope would still be the same. Likewise claim 121, 135, etc. The traverse is unpersuasive. As is noted in the discussion of "aliphatic" above, the OH is already permitted to be present in aliphatic. Thus, the optionally substituted feature does not change the scope at all, as the term is still permitted to have other substituents.
8. The term "or pharmaceutically acceptable derivative" (e.g. end of claim 2) is of unknown scope. What is a derivative? What level of change can be made in the compounds and it still be a derivative? Can the P be removed? The traverse is

unpersuasive. Applicants point to the material at page 8, line 36 to page 9, line 17. This is so open-ended as to be of no value. It covers any derivative that, in the body of the patient, is converted back into the parent compound, into a metabolite --- whatever that might be, or into a "residue", whatever that is. Thus, a derivative is a compound which the body will turn into a "residue", which is a useless concept. It also covers a compound which the body will turn into a metabolite of the original compound. However, there is no way of getting a complete list of metabolites, and even if there were such a list, how would one know which other compounds could also make such a metabolite. There is thus no reason to think that the P cannot be removed. Removal, after all, would give a "residue".

9. Further, claim 1 makes no provision for such derivatives, so claim 2 is improperly dependent on claim 1. The response misses the point. The derivatives feature is in claim 2, but not in claim 1. Regardless of how broadly the P-containing moieties are set forth in claim 1, the derivative could just as well be derived from somewhere else in the molecule.

10. The sulfate moiety is divalent, as in the well known compound dimethyl sulfate, where the two valencies are taken up by the two methyl groups. The structure in section 24.3 of reference B is not actually the sulfate, but a stem name ending with the word sulfate. In the first, what is depicted is <u>not</u> the sulfate group, but the galactopyranose-sulfate group, which does have just one valence. The reference to Exhibit G is not understood, as the issue is not addressed there.

11. The intended scope of "Phosphorous containing moiety" is unclear. Could this include a cationic substituent which had a phosphate anion as a counterion, or an

anionic substituent (e.g. carboxylate) with a phosphonium cation as a counterion? Would it include P atoms without functional groups, such as $-PO_2$ or phosphazene rings? Would it include highly reactive groups such as $-PCl_2$? The specification discussion is completely open-ended and does not discuss these issues. The traverse is unpersuasive. Applicants in their remarks repeated the examiner's questions, but have not answered a single one of these very simple questions. Their inability to do so is clear evidence of the indefiniteness. Applicants refer to "numerous examples" as providing guidance, but they have not said exactly how these examples provide guidance. There are no examples to any of the types that the examiner asked about? Does that mean that none of them are actually included? If that is not the case, then how can the examples be said to provide guidance?

12. In "protected forms" (e.g. at page 127, line8) protecting against what? These are final products, so what is there to protect against? As there is no such thing as a universal protecting group, correct selection of a protecting group requires some knowledge of what is being protected against. The traverse is unpersuasive. It is correct that many protecting groups are known. But whether something is or is not a protecting group depends on what is being protected against. Ordinarily, this is not a problem, since the reaction conditions make it clear what is to b protected against. But it is unknown what these are here, nor do the remarks give any indications of what these are

13. The fix of the definition of M has taken care of one problem but caused another. The fix does not work for iv, v and vi when x is other than 1. It only says that "one M is CV or N" But <u>every</u> M is shown as trivalent in these 3 choices, and therefore, <u>every</u>

M choice must be trivalent. Please note that in e.g. choice v, if x = 6, then the group has 6 valences, one for each M.

14. The last two claim 140 choices are not alkyl, but cycloalkyl, so that the claim is improperly dependent on claim 139. The traverse is unpersuasive. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The meaning quoted by applicants are not the usual meaning at all. Alkyl is a group of the formula $-C_nH_{2n+1}$, and as such it cannot have rings. The correct term is cycloalkyl and that is what should be used.
15. Claim 7's "additionally substituted with 0-3 substituents" makes no sense. If the number is zero, then it is not additionally substituted. The traverse is unpersuasive. The remarks state that applicants intend either unsubstituted, or 1-3 additional substituents, but that is not what the claim actually says.

Claims 7-18, 21, 26, 90, 114, 129, 178-179 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since sulfate is intended as an anionic choice as depicted on the top of page 99 of the remarks, this will produce a charged compound with a net charge of –1, as no cation is provided. Such is impossible. A compound cannot exist with a net charge of –1. The traverse is unpersuasive. What happens to the compound in solution is not the point. The fact that the two separate parts of the molecule move away from each other does not change the fact that there has to be two separate parts to begin with, before the

molecule is dissolved. The remarks thus refer to "its cation", but the claim does not provide for a cation.

Claims 176-182 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Prevention and treatment of "disorders involving bone metabolism" generally is not enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. There are four substituents present on the purine nucleus, and each is defined extremely broadly. The genus thus easily covers trillions of compounds.

(b) Scope of the diseases covered. The scope is immense. In this regard, it is noted that applicants have switched from "bone related disorders" or "disorders involving bone metabolism". This does not constitute a significant narrowing of the claims. The term "metabolism" is extremely broad. Metabolism is the physical and chemical processes by which living organized substance is produced and maintained (anabolism), and also the transformation by which energy is made available for the uses of the organism (catabolism). Thus, this covers any disorder in any physical or chemical process in which the bone is produced or maintained. There are numerous metabolic processes in bones. There are the water, calcium, phosphate, carbonate, fluoride, sodium and magnesium metabolic processes, as these are the inorganic components of bone. There are also metabolic processes needed to generate type I collagen and certain noncollagenous proteins, along with assorted glycoproteins, proteoglycans, peptides, carbohydrates, and even lipids which are found in bone. There are the numerous processes involved in the formation and activities of chondrocytes, osteoblasts, osteocytes, Haversian Canals, osteoclasts, etc. Many hormonal processes are involved in the metabolism of bones. This claim language covers nearly all bone problems except perhaps for those caused by infectious agents.

In this regard, the examiner notes on page 97 of the remarks the statement that "Applicants specification indicates that the term "bone metabolism" refers to the balance between the formation of bone tissue by osteoblasts and the resorption of bone tissue by osteoclast (page 1, lines 23-28 of the specification.)" This is simply not true. The term "bone metabolism" does not appear in the indicated text, or indeed, anywhere

on the page. Those two sentences, which are only part of the background of the invention, talk generally about a need for balance between two particular processes.

The term thus includes common bone disorders such as Paget's disease, hereditary multiple exostosis, and osteoporosis. It also includes Dysplasias including Osteogenesis imperfecta, Osteopoikilosis, Osteopetrosis (Albers-Schoenberg disease), achondroplasia, Osteochondromatosis, Caffey's disease, Lenz-Majewski syndrome, Melorheostosis, metaphyseal dysplasia (Pyle disease), pyknodysostosis, sclerosing diaphyseal dysplasia (Camurati-Engelmann Disease), spondyloepiphyseal dysplasia and many others. It includes dense bones disorders, including axial osteomalacia, fibrogenesis imperfecta ossium, sarcoidosis and tuberous scelrosis. Other bone disorders include cleidocranial dysostosis, coxa plana, Hand-Schueller-Christian disease, brachydactyly, calcium pyrophosphate deposition disease (CPPD), Wormian bones, tibia vara (Blount disease), cervical spine fusion (ankylosis), Crouzon syndrome, slipped capital femoral epiphysis (SCFE), celery-stalk metaphyses, Bankart deformity, Ollier disease, craniosynostosis, Erlenmeyer flask deformity, ivory vertebral body, spheroid calcification, acro-osteolysis, Caffey disease, cherubism, Sever disease, Sprengel deformity, Panner disease, osteogenesis imperfecta, Letterer-Siwe disease, Pott's disease, Scheuermann disease, sabre-shin deformity, basilar invagination, degenerative disc disease, block vertebra, Kohler disease, hyperostosis frontalis interna, diastrophic dwarfism, osteochondrosis, posterior vertebral scalloping, multicentric reticulohistiocytosis, osteitis fibrosa, vertebra plana, Hill-Sachs deformity, Kienbock disease, spontaneous osteolysis, Osteochondritis dissecans, and many, many more. Included also are bone tumors, including Osteosarcomas (osteoblastic, chondroblastic,

fibroblastic, telangiectatic, and others), Hemangiosarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma, reticulum cell sarcoma, malignant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma, and Multilobular tumor of bone. There are also tumor-like lesions, including osteoid Osteoma, non-osteogenic Fibroma, benign osteoblastoma, Solitary bone cyst, Juxtacortical bone cyst, Myositis ossificans, Villonodular synovitis and Epidermoid cyst of the phalanx. There are also secondary malignant deposits in bone.

In addition, the "disorders involving" substantially increases the scope of the claim. If a bone metabolism disorder causes disorder B, then disorder B is a disorder involving said bone disorder, since causation is a form of involvement. For example, the rib cage provides protection for organs located in the thoracic region, such as the heart and lungs, as well as abdominal organs, such as the liver and kidneys. It is also a primary site of hemopoiesis, the formation of blood cells, in the adult, which occurs in the red marrow of the long bones, as well as in the flat bones such as the sternum, the ribs, the ileum, and the vertebral bodies. The cartilage-covered ends of the bone form articulate joints to allow multiplication of the force of the attached muscles. Thus, if a bone disorder disrupts e.g. hemopoiesis, that hemopoietic disorder will certainly fall within the scope of this claim. Similarly, the claim now covers disorders such as rheumatoid arthritis, a disorder which involves osteoclast formation. It would also cover

disorders which are "upstream" of the bone problem. Thus, if a person had a gastrointestinal disorder that prevented a person from absorbing calcium from food, that would certain involve bone metabolism as a cause for the bone metabolism disorder.

(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information given in the sentence bridging pages 50-51 is not associated with any particular disease. Only a few bone diseases are mentioned specifically.

(4) State of the Prior Art: One skilled in the art knows that bone disorders can arise from a huge assortment of unrelated causes. These include Ehlers-Danlos syndrome, galactosemia, cirrhosis, vitamin D malabsorption arising from GI disorders such as celiac disease, from pancreatic insufficiency, from biliary atresia and other sources, abnormal vitamin D metabolism arising from e.g. anticonvulsant therapy, chronic renal failure, etc., hyperparathyroidism and hypoparathyroidism and pseudohypoparathyroidism, Marfan syndrome, fluorosis (excessive fluoride intake), ochronosis, lead poisoning, cadmium poisoning, Morquio's disease, Cushing's disease, Gaucher disease, tyrosinemia, homocystinuria, scurvy, ToRCHS syndrome, renal osteodystrophy, Hypertrophic osteoarthropathy, Klippel-Feil syndrome, sickle cell

anemia, glycogen storage disease, Niemann-Pick disease, hyperuricemia, renal transplantation, hemophilia, gout, histiocytosis X, Tuberculosis, hypervitaminosis A and D, frostbite, burns, leprosy, polyvinylchloride exposure, progeria, acromegaly, basal cell nevus syndrome, Erdheim-Chester disease, psoriasis, Ligna-Franconi Diseasesteroids, shoulder dislocation, juvenile rheumatoid arthritis, Wilson's Disease, hypophosphatasia and pseudo hypophosphatasia, ingestion of phosphate binding antacids, and of mineralization inhibitors such as Etidronate, dietary deficiencies in phosphate and calcium, brain tumors, alcohol abuse, bone fracture, diabetes, caisson disease, hemodialysis, milk-alkali syndrome, carbonic anhydrase II deficiency and many, many more. The secondary malignant deposits in bone arise from primary malignancies in the thyroid, breast, bronchus, kidney and prostate. There are a wide assortment of genetic problems, many of them poorly understood, which cause bone disorders. And sometimes, the cause is unknown. For example, Paget's disease is the second most common disorder of the bone, and its origin is unknown. All of these involve at one stage or another, metabolic processes of the bone.

(5) Working Examples: There are no working examples for the treatment of any disorder. Assorted tests are mentioned, but no data is provided for any specific compounds.

(6) Skill of those in the art: The skill level varies greatly according to which disorder is involved. For e.g. osteoporosis the skill level is good. For many others, the skill level is extremely low, as there have been no successful pharmacological treatments. An example is the assorted osteosarcomas; no chemotherapy has even been demonstrated as a successful mode. Further, the skill level for prevention, which is mentioned in

claims 180-181, is much lower still. Even some which can be treated, e.g. Paget's, cannot be prevented from occurring in the first place.

(7) The quantity of experimentation needed: In view of the extreme diversity of such disorders, the extreme breadth of the genus of compounds, the known difficulty of treating bone disorders with medicinals, the level of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. As noted above, applicants are reading limitations into the claims which simply are not present. Applicants also state, "For some diseases involving bone metabolism, the underlying case and risk factors for the disease are well known." Agreed, although knowledge of risk factors (e.g. smoking, lack of exercise, etc) is not directly relevant to enablement. But the claims are not limited to those limited number of bone disorders. Applicants argue that they have amended the claims so that the compounds used "are those that inhibit the activity of osteoclasts". However, a) the way e.g. claim 176 is worded, the scope is defined by Formula I; Claim 176 says, "wherein the compound has the formula....". The claim simply adds the fact that all such compounds inhibit the activity of osteoclasts. Formula I in fact covers all the compounds of the invention; it is the broadest genus, b) the claim is not limited to disorders

involving osteoclasts. Regardless of the scope of the compounds themselves, the scope of diseases is not so limited in any claim. It would cover for example disorders in which osteoblast formation is too high or too low. Indeed, the claim language covers disorders in which the osteoclast activity is already too low and one needs to induce osteoclast formation. The entire thrust of applicants' arguments is thrust oriented toward a view of the claims which is much more limited than what actually occurs.

With regard to prevention, which is present in claims 180-181, the exact same problems arise.

Claims 176-182 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As noted above, the new "disorders involving" substantially increases the scope of the claim beyond what the specification has, since it now deals with disorders which are not necessarily bone problems at all, so long as they are in some way "related".

Claims 184-195 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

These claims call for the treatment of cancer and tumors generally.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation

is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. There are four substituents present on the purine nucleus, and each is defined extremely broadly. The genus thus easily covers trillions of compounds.

(b) Scope of the diseases covered. The coverage is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information given in the sentence bridging pages 50-51 is not associated with any particular disease. No specific cancers are named in the specification.

(4) State of the Prior Art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. In addition, note that these compounds are adenine derivatives. So far as the examiner is aware, adenines have never been used to treat cancer.

(5) Working Examples: There are no working examples for the treatment of any disorder. Assorted tests are mentioned, but no data is provided for any specific compounds.

(6) Skill of those in the art: It is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available.

(7) The quantity of experimentation needed: In view of the extreme diversity of such disorders, the extreme breadth of the genus of compounds, the known difficulty of getting anti-cancer compounds to actually work, the level of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants' argument seems to be that any inhibitor of any tyrosine kinase (and there are dozens) can treat any cancer. If this were true of course there would be no cancers left to treat, since there are thousands of compounds which have been discovered which inhibit assorted tyrosine kinases. Exactly the opposite is true. As of the filing date, There was exactly one such agent found to be effective against cancer, Herceptin, which is a monoclonal antibody (not the technology here) which affects one receptor, ErbB-2. In fact, the reference which applicants supplied, Morin et al, says at the top of page 6581, "It is clear that the development of newer agents like tyrosine kinase inhibitors will require new concepts and clinical paradigms that are distinctly different from those used to develop the well-known cytotoxic agents commonly used in cancer chemotherapy ... Paramount among these is the need for non-conventional endpoints in clinical drug design, and for the identification, validation and implementation of surrogate endpoints" It is clear from

this that as of 2000, tyrosine kinase inhibitors would involve extensive experimentation to figure out how to get to work, since such fundamentals like conventional endpoints could not be used. The extreme difficulty of getting tyrosine kinase inhibitors to work against cancer can be seen in the case of Iressa®, which is discussed extensively in this reference. A tremendous amount of work by AstraZeneca has been devoted to this drug. Yet, even as of the present day, all attempts to get this to actually work against lung cancer have failed, as tests unequivocally failed to demonstrate clinical benefit. This is clear evidence of the low skill level in this art. In contrast, applicants claim that their trillions of compounds can be used against all cancers, on the basis of a specification which does not contain a single test of any specific compound against any actual cancer or cancer cell line. Simply describing a conventional assay, such as appears on page 118, does not demonstrate enablement.

Claims 2-7, 10, 13-20, 22-28, 30-62, 64-89, 91-98, 100-116, 118-175, 177-178, 180-183, 185-189, 191-259 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The new claim 2 choices of M as CV and N are new matter. It is clear that a trivalent choice is needed, but it is not clear that these two, as opposed to just one of them, or as opposed to other trivalent choices like CH or P or B were intended. The same is true in claim 125, where applicants have added CH, C-Hal, and C-OH as choices, which trio of

choices lacks description in the specification. Likewise in claims 20, 55, 89, 108, 158, 177, 180-181, 185-186, and 191-192.

Claims 31, 65, 134, 198, and 224 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

B. The replacement of "thio" with SH (the mercapto group) is new matter. As a substituent, it has no one single generally accepted meaning. There could be intended thioxo (=S) or mercapto (-SH). If it denotes replacement by S of some other atom as in "thioalkoxy", then the rest of the term is missing; was "thioalkoxy" intended? Perhaps some other term which began with "thio", like thiophene was intended. The remarks in the paragraph bridging pages 96-97 point to the specification, page 20, line 27 to page 21, line 10, noting that for one of the groups, when p = 0, it becomes the SH group. This is true, but applicants have not explained why this makes the SH group the thio. If any of the next three choices had their p set as zero, then a group different from SH would have resulted.

Specification

The amendment to page 6 is objected to as containing new matter, for the reasons set forth in point A above.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical

subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 10, 13-28, 32-35, 40-62, 64-98, 100-116, 118-259 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18, 35-39 of copending Application No. 09/740393. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons given previously.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

10/17/2003